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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/935,168	WEST ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-9 and 24-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-9 and 24-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/16/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-5, 7-9, and 24-35 are pending.

2. In view of the amendment filed 1/30/06, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 24-35 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method for making a tissue engineering scaffold as set forth in claims 1-5, 8 and 9, **does not** reasonably provide enablement for a method for making a tissue engineering scaffold using any matrix-enhancing molecule, any matrix-enhancing molecule such as TGF beta, angiotensin II, insulin like growth factor and ascorbic acid at any concentration sufficient to elicit production of any extracellular matrix by any cell, any cell such as smooth muscle cells, endothelial cells, fibroblasts, chondrocytes, and any combination thereof attached to any engineering scaffold without increasing cellular proliferation of the attached cells as set forth in claims 24-35. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only TGFbeta at optimal concentration in the range of between one and five ng TGF-β/ml, which is equivalent to between 4×10^{-6} and $4x\ 10^{-3}$ nmol/ml

covalently coupled to hydrogel via polyethylene glycol for inducing extracellular matrix production by aortic smooth muscle cells.

The specification does not teach how to make all "matrix-enhancing molecule" for the claimed method without the amino acid sequence. Given the unlimited number of matrix enhancing molecules, there is insufficient guidance as to which matrix enhancing molecules would induce the production of which extracellular matrix by which cell type without increasing cellular proliferation of the attached cells to the scaffold, much less at which particular concentration for the claimed method. Further, there is insufficient working example showing that any matrix enhancing molecule is effective for inducing matrix production in all cell type, in turn, would be useful for implantation. The specification does not teach how to predict which matrix-enhancing molecule is effective for inducing matrix production by which cell type.

Stryer et al teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Given the unlimited number of matrix enhancing molecules and without the structure (i.e. chemical structure of amino acid sequence), it is unpredictable which undisclosed matrix-enhancing molecule at which concentration is effective for inducing which matrix production for the claimed method.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 1/30/06 have been fully considered but are not found persuasive.

Applicants' position is that a skilled artisan does not need to know the amino acid sequence of a particular matrix-enhancing molecule to make and use the claimed methods. In fact, some matrix-enhancing molecules do not even have an amino acid sequence, for example,

ascorbic acid. Applicants have enabled matrix-enhancing molecules. One source of guidance may be found in Applicants' independent claim 24 itself, which recites that 'The matrix-enhancing molecule . . . elicits production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cell." Applicants' disclosure provides -examples of four suitable matrix enhancing molecules. See Application paragraph 27-29. Moreover, suitable matrix-enhancing molecules are well known in the art, as the art cited by the Examiner shows. See, e.g., '430 Patent, col. 6, 11. 55-66; '849 Patent, col. 16, Table 1. Regarding guidance for "which cell type, such is provided by Applicants' specification, as well as by what well known to those skilled in the art. Applicants' specification provides examples of various cell types, as well as sources of such cells, see ¶ 28. Applicants have enabled concentrations of matrix-enhancing molecules. First, the claim language itself provides the concentration of the matrix enhancing molecules: "sufficient to elicit production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cell". Applicant's specification also describes that "the optimal density of the matrix molecule will depend on the type of cells to be attached to the scaffold." The specification teaches how a skilled person could determine a particular with reference to TGF-β and ascorbic acid. See application ¶ 29, 43-77-79. Applicants' specification provides working examples, and to the extent any experimentation is needed, a skilled person would not considered it undue.

In response, the claims encompass a method of making a tissue engineering scaffold covalently coupling any polymer tether to any scaffold and then covalently coupling any matrix-enhancing molecule at any concentration sufficient to elicit production of any extracellular matrix by any cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cells. The specification defines matrix-enhancing molecule at page 6 as any glycoproteins, any glycoproteins such as elastin, collagen, TGF-β, agniogensin II, insulin-like growth factors, and ascorbic acid. The specification defines "scaffold materials" at page 5 as any synthetic or natural polymers, such as hydroxyapatide, silicone, and other inorganic materials can be used. The specification defines "Tethers" at page 7 as any polymer having a molecule weight of between about 200 and 10,000, most preferably between 2000 and 6,000. The specification defines the cells at page 7 last paragraph as human muscle cells from a donor, from a culture cells or from established cell lines. The preferred cells for formation of connective tissue include

chondrocytes, fibroblasts, and other types of cells that differentiate into bone or cartilage (see page 8, lines 6-10).

The specification does not teach how to make any and all tissue engineering scaffold using any "matrix-enhancing molecule", any scaffold and any polymer tether. This is because definition of matrix-enhancing molecule at page 6 of the specification is any glycoproteins. The "glycoproteins" without the amino acid sequence has no structure, much less function. Further, there is a lack of guidance as to the concentration, i.e., nmol/ml of any and all glycoproteins, any glycoprotein such as angiotensin II and insulin-like growth factor that elicit the production of which extracellular matrix by which cell type attached to tissue engineering scaffold. Even if the cells are smooth muscle cells, endothelial cells, fibroblasts, chondrocytes and combination thereof, it is known that TGF-beta increases production of extracellular matrix proteins by vascular smooth muscle cells (see page 6 of specification). The same TGFbeta glycoprotein has different effects on different cell types such as induces the proliferation of cardiac fibroblasts and their phenotypic conversion to myofibroblasts, the deposition of extracellular matrix (ECM) proteins such as collagen, fibronectin, and proteoglycans, and hypertrophic growth of cardiomyocytes. Although the structure of matrix-enhancing molecule and concentration are recited in Claims 28 and 29, the structures of the scaffold and polymer are not enabled in the claimed method. Given the unlimited number of undisclosed glycoproteins as matrix-enhancing molecules covalently attached to any scaffold via any polymer tether attached by any number of cell to the tissue engineering scaffold in the claimed method, it is unpredictable which undisclosed glycoproteins as matrix-enhancing molecule is useful for making tissue engineering scaffold, in turn, would be useful for enhance the production of which extracellular matrix by which cell type. Accordingly, it would require undue experimentation to determine how to practice the invention as it is drawn to a method of making any tissue engineering scaffold using any matrix-enhancing molecules other than TGF-beta and ascorbic acid.

5. Claims 24-35 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any matrix-enhancing molecule, any matrix-enhancing molecule such as angiotensin II, insulin like growth

factor and ascorbic at any concentration sufficient to elicit production of (2) any extracellular matrix by (3) any cell attached to any engineering scaffold.

The specification discloses only TGFbeta at optimal concentration in the range of between one and five ng TGF-β/ml, which is equivalent to between 4 x 10^{-6} and 4x 10^{-3} nmol/ml covalently coupled to hydrogel via polyethylene glycol for inducing extracellular matrix production by aortic smooth muscle cells.

With the exception of the specific matrix-enhancing molecule to eliciting matrix production in only smooth muscle cells for the claimed method, there is insufficient written description about the structure associated with function of all matrix-enhancing molecule to induce matrix production in any other cells for the claimed method. Given the unlimited number of matrix-enhancing molecule, the concentration effective for each undisclosed matrix-enhancing molecule for which cell type for the claimed method is not adequately described.

The specification discloses only a method of making tissue engineering scaffold using only TGFbeta covalently coupled to PEG-diacrylate hydrogel, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of matrix-enhancing molecule to describe the genus for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 1/30/06 have been fully considered but are not found persuasive.

Applicants' position is that Applicants have described matrix-enhancing molecules (page 13 of amendment). Applicants' specification states that "matrix-enhancing molecules which promote increased production of ECM can be attached to the scaffold material to induce production of matrix proteins . . . without substantially increasing cell proliferation. These matrix-enhancing molecules include TGFβ, angiotensin II, insulin-like growth factors and ascorbic acid." See Application ¶28. Applicant's specification also discloses that the concentration for a specific matrix-enhancing molecule "will depend on the type of cell to be attached to the scaffold." Application ¶34. Moreover, Applicant's specification provides exemplary concentrations of matrix-enhancing molecules. For example, the concentration of the matrix-enhancing molecule

TGFβ needed to elicit ECM production in articular chondrocytes is provided. Application ¶34. Furthermore, independent claim 24 provides the concentration of the matrix enhancing molecules: "sufficient to elicit production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cell".

In response, the claims encompass a method of making a tissue engineering scaffold covalently coupling any polymer tether to any scaffold and then covalently coupling any matrix-enhancing molecule at any concentration sufficient to elicit production of any extracellular matrix by any cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cells. None of the claims are drawn to the specific matrix-enhancing molecule as argued. Further, the specification does not adequately describe the concentration, i.e. ng/ml or nmol/ml of enhancing molecule such as angiontensin II, insulin-like growth factor and ascorbic acid sufficient to elicit the production of which extracellular matrix by which cell attached to the tissue engineering scaffold for the claimed method.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 24, 28, 31 and 35 stand rejected under 35 U.S.C. 102(b) as being anticipated by US Pat 5,162,430 (Nov 10, 1992; PTO 892).

The '430 patent teaches a method of making a tissue engineering scaffold by providing a scaffold such as collagen (col. 4, lines 5-6, in particular) covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol (see PEG, col. 5, lines 32-55, in particular) covalently coupled to a matrix enhancing molecule such as TGFbeta (col. 6, line 58, see entire document, col. 8, General Method, Examples 1 and 6, col. 19, in particular) or insulin like growth factor or combination thereof (see col. 6, line 63, in particular). The reference polyethylene glycol has a molecular weight of between 1900, and about 8,000, which is between the claimed 200 and 10,000 (see col. 5, line 39, in particular). The reference tissue engineering is useful for tissue or organ implantation or tissue regeneration (see col. 4, line 28-40, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 1/30/06 have been fully considered but are not found persuasive.

Applicants' position is that the'430 patent does not teach "the matrix-enhancing molecule is present at a concentration sufficient to elicit production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cell" as recited in independent claim 24.

In response, the specific concentration such as ng/ml or nmol/ml of the specific matrix-enhancing molecule is not recited in independent claim 24. Further, the specific type of cell attached to the engineering tissue scaffold that affected by the specific matrix enhancing molecule is not recited in claim 24.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-2, 4, 8 and 9 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat 5,162,430 (Nov 10, 1992; PTO 892) in view of Dinbergs *et al* (of record, J Biol Chem 271(47): 29822-29, 1996; PTO 892).

The '430 patent teaches a method of making a tissue engineering scaffold by providing a scaffold such as collagen (col. 4, lines 5-6, in particular) covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol (see PEG, col. 5, lines 32-55, in particular) covalently coupled to a matrix enhancing molecule such as TGFbeta (col. 6, line 58, see entire

document, col. 8, General Method, Examples 1 and 6, col. 19, in particular) or insulin like growth factor or combination thereof (see col. 6, line 63, in particular). The reference polyethylene glycol has a molecular weight of between 1900, and about 8,000, which is between the claimed 200 and 10,000 (see col. 5, line 39, in particular). The reference tissue engineering is useful for tissue or organ implantation or tissue regeneration (see col. 4, line 28-40, in particular).

The claimed invention in claim 1 differs from the reference only in that the method wherein the TGF-beta is present at a density of between 1 and 100 ng/ml or in a concentration of between about 4×10^{-6} and 4×10^{-3} nmol/ml.

Dinbergs *et al* teach a method for making a tissue engineering scaffold such as alginate/heparin-sepharose microsphere for inducing formation of extracellular matrix by cells such as endothelial cells and smooth muscle cells bound to said scaffold comprising coupling various matrix-enhancing molecule such as bFGF or TGFβ in a concentration 1-10 ng/ml (See Alginate/Heparin-Sepharose Microsphere Preparation and Growth Factor Incorporation, page 29823, column 2, bridging page 29824 column 1, in particular). The reference TGFβ is effective to elicit production of extracellular matrix (see page 29822, column 2, last paragraph, in particular) without increasing cellular proliferation (See Fig 2B, Fig 3B, Abstract, in particular). Dinbergs *et al* teach TGFβ has been incorporated into scaffold or various biodegradable polymer matrix such as collagen, hydrogel such as alginate, hydron (hyaluronic acid) and polyethylene glycol polymers (See page 29827, column 2, first full paragraph, in particular). Dinbergs *et al* teach TGFβ is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use TGFbeta a concentration 1-10 ng/ml as taught by Dinbergs *et al* for a method of for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells such as smooth muscle cell or endothelial cells where the TGF is covalently coupled to collagen or alginate via a polymer tethered as taught by the '430 patent and Dinbergs *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Dinbergs *et al* teach TGFβ has been incorporated into scaffold or various biodegradable polymer matrix such as collagen, hydrogel such as alginate, hydron (hyaluronic acid) and polyethylene

glycol polymers (See page 29827, column 2, first full paragraph, in particular). Dinbergs *et al* teach TGFβ is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular). The method of tissue engineering is useful for tissue or organ implantation or tissue regeneration as taught by the '430 patent (see col. 4, line 28-40, in particular).

Applicants' arguments filed 1/30/06 have been fully considered but are not found persuasive.

Applicants' position is that the examiner has not provided a sufficient teachings, suggestion, or motivation in the prior art to make such a combination. Applicants further submit that an ordinary artisan at the time of applicants' invention would not have had a reasonable expectation that the proposed '430 patent and Dinbergs combination would succeed. Applicants asserts that the Examiner has not considered the cited references and Applicants' invention as a whole, and used improper hindsight reconstruction to make the proposed '430 patent and Dinbergs combination.

In response to applicants' argument that there is no suggestion to combine the references, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In this case, the teachings of Dinbergs *et al* pertaining to TGFβ has been incorporated into scaffold or various biodegradable polymer matrix such as collagen, hydrogel such as alginate, hydron (hyaluronic acid) and polyethylene glycol polymers and is useful for eliciting extracellular matrix formation *without increasing cellular proliferation* for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular), the teachings of the '430 patent pertaining to a method of making a tissue engineering scaffold by providing a scaffold such as collagen (col. 4, lines 5-6, in particular) covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol (see PEG, col. 5, lines 32-55, in particular) covalently

coupled to a matrix enhancing molecule such as TGFbeta (col. 6, line 58, see entire document, col. 8, General Method, Examples 1 and 6, col. 19, in particular) or insulin like growth factor or combination thereof (see col. 6, line 63, in particular) would have led one of ordinary skill in the art at the time the invention was made to make any tissue engineering scaffold with the expectation that at such concentration as taught by Dinbergs et al, it would elicit extracellular matrix formation without increasing cellular proliferation.

In response to applicants' argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 170 USPQ 209 (CCPA 1971).

11. Claim 3 stands rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat 5,162,430 (Nov 10, 1992; PTO 892) in view of Dinbergs et al (of record, J Biol Chem 271(47): 29822-29, 1996; PTO 892) as applied to claims 1-2, 4, 8 and 9 and further in view of Scott-Burden et al (J Cardiovasc Pharmacol 16 Suppl 4: S36-41, 1990; PTO 892).

The combined teachings of the '430 patent and Dinbergs et al have been discussed supra.

The claimed invention in claim 3 differs from the teachings of the references only in that the method wherein the matrix-enhancing molecule is angiotensin II.

Scott-Burden et al teach angiotensin II activates the synthesis of extracellular matrix such as glycopeptides and proteoglycans by smooth muscle cells and growth of smooth muscle cell (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the TGF beta as taught by the '430 patent and Dinbergs et al for the angiotensin II as taught by Scott-Burden et al for a method of for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells such as smooth muscle cell where the angiotensin II is covalently coupled to collagen via a polymer tethered such as PEG as taught by the '430 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because angiotensin II activates the synthesis of extracellular matrix such as glycopeptides and proteoglycans by smooth muscle cells as well as the growth of smooth muscle cell as taught by Scott-Burden et al (see abstract, in particular). Dinbergs *et al* teach TGFβ is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular). The method of tissue engineering is useful for tissue or organ implantation or tissue regeneration as taught by the '430 patent (see col. 4, line 28-40, in particular).

Applicants' arguments filed 1/30/06 have been fully considered but are not found persuasive.

Applicants' position is that claims 3, 5, 7 and 8 depend either directly or indirectly from independent claim 1. All these dependent claims, which include all the limitations of claim 1, are allowable for at least the reasons cited above with respect to independent claim 1.

In response, the responses to applicants' arguments with respect to claim 1 have been discussed supra and are incorporated here by reference.

12. Claims 5, 7 and 8 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat 5,162,430 (Nov 10, 1992; PTO 892) in view of Dinbergs *et al* (of record, J Biol Chem 271(47): 29822-29, 1996; PTO 892) as applied to claims 1-2, 4, 8 and 9 and further in view of US Pat No. 5,935,849 (Aug 10, 1999; PTO 892).

The combined teachings of the '430 patent and Dinbergs et al have been discussed supra.

The claimed invention in claim 5 differs from the teachings of the references only in that the method wherein the matrix-enhancing molecule is ascorbic acid.

The claimed invention in claim 7 differs from the teachings of the references only in that the method wherein the scaffold is a hydrogel.

The claimed invention in claim 8 differs from the references only in that the method wherein the scaffold hydrogel is alginate and combination thereof.

The '849 patent teaches a method of making a tissue engineering scaffold such as bioartificial organ (BAO) using scaffold such as hydrogel or alginate or collagen (see col. 19, lines 22, col. 20, lines 42-36, summary of invention, in particular) covalently coupling to an inner matrix by a tether such as poly-d-lysine (see col. 18, line 30-35, in particular) coupling to matrix enhancing molecule such as RGD containing sequence (see col. 18, lines 36-51, in particular) or

TGF beta and/or ascorbic acid (see col. 12, line 56-67, in particular). The '849 patent teaches TGF beta is useful for inducing differentiation of fibroblast cells, and also as a growth inhibitor of keratinocytes and endothelial cells while ascorbic acid and TGFbeta1 increase collagen biosynthesis (see col. 12, lines 57-67, Table 1, in particular). The reference method further comprises providing cells such as fibroblast or endothelial cells attached within the tissue-engineering scaffold (see col. 16, Table 1, Col. 19, line 29, in particular). The reference method is useful for implantation and controlling distribution of cells within the bioartificial organ (see claims of '849 patent).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the collagen and TGF beta in the tissue engineering scaffold comprising collagen covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol and matrix enhancing molecule such as TGFbeta as taught by the '430 patent for the hydrogel such as alginate and ascorbic acid as taught by the '849 patent for a method of making a tissue engineering scaffold comprising the hydrogel such as alginate covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol and matrix-enhancing molecule such as TGFbeta and/or ascorbic acid as taught by the '430 patent, Dinbergs et al and the '849 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because TGF beta is useful for inducing differentiation of fibroblast cells, and also as a growth inhibitor of keratinocytes and endothelial cells, while ascorbic acid and TGFbeta1 increase collagen biosynthesis as taught by the '849 patent (see col. 12, lines 57-67, Table 1, in particular). The use of engineering scaffold is useful to control cell number, cell distribution and attachment in organ transplant as taught by the '849 patent. Dinbergs *et al* teach TGFβ is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular). The method of tissue engineering is useful for tissue or organ implantation or tissue regeneration as taught by the '430 patent (see col. 4, line 28-40, in particular).

Applicants' arguments filed 1/30/06 have been fully considered but are not found persuasive.

Applicants' position is that claims 3, 5, 7 and 8 depend either directly or indirectly from independent claim 1. All these dependent claims, which include all the limitations of claim 1, are allowable for at least the reasons cited above with respect to independent claim 1.

In response, the responses to applicants' arguments with respect to claim 1 have been discussed supra and are incorporated here by reference.

13. Claim 8 stands rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat 5,162,430 (Nov 10, 1992; PTO 892) in view of Dinbergs *et al* (of record, J Biol Chem 271(47): 29822-29, 1996; PTO 892) as applied to claims 1-2, 4, 8 and 9 and further in view of WO 94/23740 (of record, Oct 1994, PTO 1449) or WO 96/27657 (Sept 1996; PTO 1449).

The combined teachings of the '430 patent and Dinbergs et al have been discussed supra.

The claimed invention in claim 8 differs from the teachings of the references only in that the method wherein the scaffold is a hyaluronic acid or polyethylene glycol polymer instead of collagen.

The WO 94/23740 publication teaches a method for making a tissue engineering scaffold comprising coupling various matrix-enhancing molecules such as TGFβ or TGFβ2 covalently coupling to polyethylene glycol (See page 12, line 11, PEG-TGF-β conjugates, rhTGF- TGF-β2 (PEG5000) bridging page 13, in particular). The WO 94/23740 publication teaches the method of making a tissue engineering scaffold comprising coupling TGFβ to a polymer is useful for stimulation of bone formation at a lower dose (See abstract, in particular).

The WO 96/27657 publication teaches a method for making a tissue engineering scaffold comprising coupling various matrix-enhancing molecules such as TGFβ (see page 10, claim 25 of WO 96/27657 publication, in particular) covalently coupled to a scaffold such as hyaluronic acid (see page 7, line 1, in particular) or polyethylene oxide, or alginate, (See page 17, line 8, in particular). The WO 96/27657 publication teaches the growth factor is localized to desired target cell population and significantly less growth factor is needed to exert a biologic response (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the collagen and TGF beta in the tissue engineering scaffold comprising collagen covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol and matrix enhancing molecule such as TGFbeta as taught by the '430 patent for the polyethylene glycol as taught by the WO 94/23740 publication or the hyaluronic acid as

taught by the WO 96/27657 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because polyethylene glycol covalently to TGFβ2 is useful for stimulation of bone formation at a lower dose as taught by the WO 94/23740 publication (See abstract, in particular). The WO 96/27657 publication teaches hyaluronic acid (see page 7, line 1, in particular) or polyethylene oxide, or alginate coupled to TGFβ is useful for localized the desired target cell population and significantly less growth factor is needed to exert a biologic response (See abstract, in particular).

Applicants' arguments filed 1/30/06 have been fully considered but are not found persuasive.

Applicants' position is that claims 3, 5, 7 and 8 depend either directly or indirectly from independent claim 1. All these dependent claims, which include all the limitations of claim 1, are allowable for at least the reasons cited above with respect to independent claim 1.

In response, the responses to applicants' arguments with respect to claim 1 have been discussed supra and are incorporated here by reference.

14. Claims 24-27 and 32-34 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat 5,162,430 (Nov 10, 1992; PTO 892) in view of US Pat No. 5,935,849 (Aug 10, 1999; PTO 892).

The teachings of the '430 patent have been discussed supra.

The claimed invention in claim 25 differs from the reference only in that the method further comprises providing cell attached to the tissue engineering scaffold.

The claimed invention in claim 26 differs from the reference only in that the method further comprises providing cell attached to the tissue engineering scaffold wherein the cell is attached within the scaffold.

The claimed invention in claim 27 differs from the reference only in that the method wherein the cell is selected from the group consisting of endothelial cells, fibroblasts, and combination thereof.

The claimed invention in claim 32 differs from the reference only in that the method wherein the matrix enhancing molecule is ascorbic acid.

The claimed invention in claim 33 differs from the reference only in that the method wherein the scaffold is a hydrogel.

The claimed invention in claim 33 differs from the reference only in that the method wherein the scaffold hydrogel is alginate, hyaluronic acid, polyethylene glycol polymers and combination thereof.

The '849 patent teaches a method of making a tissue engineering scaffold such as bioartificial organ (BAO) using scaffold such as hydrogel or alginate or collagen (see col. 19, lines 22, col. 20, lines 42-36, summary of invention, in particular) covalently coupling to an inner matrix by a tether such as poly-d-lysine (see col. 18, line 30-35, in particular) coupling to matrix enhancing molecule such as RGD containing sequence (see col. 18, lines 36-51, in particular) or TGF beta and/or ascorbic acid (see col. 12, line 56-67, in particular). The '849 patent teaches TGF beta is useful for inducing differentiation of fibroblast cells, and also as a growth inhibitor of keratinocytes and endothelial cells while ascorbic acid and TGFbeta1 increase collagen biosynthesis (see col. 12, lines 57-67, Table 1, in particular). The reference method further comprises providing cells such as fibroblast or endothelial cells attached within the tissue engineering scaffold (see col. 16, Table 1, Col. 19, line 29, in particular). The reference method is useful for implantation and controlling distribution of cells within the bioartificial organ (see claims of '849 patent).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute (1) the collagen taught by the '430 patent for the hydrogel such as alginate as taught by the '849 patent and (2) the TGFbeta taught by the '430 patent for the TGFbeta and/or ascorbic acid as taught by the '849 patent for a method of making a tissue engineering scaffold comprising the hydrogel such as alginate covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol and matrix-enhancing molecule TGFbeta and/or ascorbic acid as taught by the '430 patent and the '849 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because TGF beta is useful for inducing differentiation of fibroblast cells, and also as a growth inhibitor of keratinocytes and endothelial cells, while ascorbic acid and TGFbeta1 increase collagen biosynthesis as taught by the '849 patent (see col. 12, lines 57-67, Table 1, in particular). The use of engineering scaffold is useful for controlling the cell number, the cell distribution and attachment in organ transplant as taught by the '849 patent. The method of tissue engineering is

useful for tissue or organ implantation or tissue regeneration as taught by the '430 patent (see col. 4, line 28-40, in particular).

Applicants' arguments filed 1/30/06 have been fully considered but are not found persuasive.

Applicants' position is that the combination of the '430 patent and the '849 patent has not shown to teach the covalently coupling the matrix-enhancing molecule to the scaffold. Nowhere has the '849 Patent been shown to discuss suitable concentrations of matrix-enhancing molecules, much less "a concentration sufficient to elicit production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cell," as recited in Applicants' independent claim 24.

In response, the '430 patent teaches a method of making a tissue engineering scaffold by providing a scaffold such as collagen (col. 4, lines 5-6, in particular) covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol (see PEG, col. 5, lines 32-55, in particular) covalently coupled to a matrix enhancing molecule such as TGFbeta (col. 6, line 58, see entire document, col. 8, General Method, Examples 1 and 6, col. 19, in particular) or insulin like growth factor or combination thereof (see col. 6, line 63, in particular).

The claimed invention in claim 25 differs from the reference only in that the method further comprises providing cell attached to the tissue engineering scaffold.

The claimed invention in claim 26 differs from the reference only in that the method further comprises providing cell attached to the tissue engineering scaffold wherein the cell is attached within the scaffold.

The claimed invention in claim 27 differs from the reference only in that the method wherein the cell is selected from the group consisting of endothelial cells, fibroblasts, and combination thereof.

The claimed invention in claim 32 differs from the reference only in that the method wherein the matrix enhancing molecule is ascorbic acid.

The claimed invention in claim 33 differs from the reference only in that the method wherein the scaffold is a hydrogel.

The claimed invention in claim 33 differs from the reference only in that the method wherein the scaffold hydrogel is alginate, hyaluronic acid, polyethylene glycol polymers and combination thereof.

The '849 patent teaches a method of making a tissue engineering scaffold such as bioartificial organ (BAO) using scaffold such as hydrogel or alginate or collagen (see col. 19, lines 22, col. 20, lines 42-36, summary of invention, in particular) covalently coupling to an inner matrix by a tether such as poly-d-lysine (see col. 18, line 30-35, in particular) coupling to matrix enhancing molecule such as RGD containing sequence (see col. 18, lines 36-51, in particular) or TGF beta and/or ascorbic acid (see col. 12, line 56-67, in particular). The '849 patent teaches TGF beta is useful for inducing differentiation of fibroblast cells, and also as a growth inhibitor of keratinocytes and endothelial cells while ascorbic acid and TGFbeta1 increase collagen biosynthesis (see col. 12, lines 57-67, Table 1, in particular). The reference method further comprises providing cells such as fibroblast or endothelial cells attached within the tissue engineering scaffold (see col. 16, Table 1, Col. 19, line 29, in particular). The reference method is useful for implantation and controlling distribution of cells within the bioartificial organ (see claims of '849 patent).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute (1) the collagen taught by the '430 patent for the hydrogel such as alginate as taught by the '849 patent and (2) the TGFbeta taught by the '430 patent for the TGFbeta and/or ascorbic acid as taught by the '849 patent for a method of making a tissue engineering scaffold comprising the hydrogel such as alginate covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol and matrix-enhancing molecule TGFbeta and/or ascorbic acid as taught by the '430 patent and the '849 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because TGF beta is useful for inducing differentiation of fibroblast cells, and also as a growth inhibitor of keratinocytes and endothelial cells, while ascorbic acid and TGFbeta1 increase collagen biosynthesis as taught by the '849 patent (see col. 12, lines 57-67, Table 1, in particular). The use of engineering scaffold is useful for controlling the cell number, the cell distribution and attachment in organ transplant as taught by the '849 patent. The method of tissue engineering is useful for tissue or organ implantation or tissue regeneration as taught by the '430 patent (see col. 4, line 28-40, in particular).

Again, claim 24 does not recite the specific concentration such as ng/ml or nmol/ml of the specific matrix-enhancing molecule. Further, the specific type of cell attached to the

engineering tissue scaffold that affected by the specific matrix enhancing molecule is not recited in claim 24. Given the claimed method uses the same matrix-enhancing molecule such as TGF-beta coupled to the same scaffold such as hydrogel or alginate or collagen via the same polymer tether such as hydrophilic polymer polyethylene glycol, it is within the purview of one ordinary skill in the art to optimize the concentration of matrix-enhancing molecule for the particular cell type attached to the tissue engineering scaffold to elicit production of extracellular matrix without increasing cellular proliferation of the attached cell.

15. Claims 27 and 29 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat 5,162,430 (Nov 10, 1992; PTO 892) in view of 5,935,849 (Aug 10, 1999; PTO 892) as applied to claims 24-27 and 32-34 mentioned above and further in view of Dinbergs *et al* (of record, J Biol Chem 271(47): 29822-29, 1996; PTO 892).

The combined teachings of the '430 patent and the '849 patent have been discussed supra.

The claimed invention in claim 27 differs from the references only in that the method wherein the cell is smooth muscle cells.

The claimed invention in claim 29 differs from the references only in that the method wherein the TGF-beta is present at a density of between 1 and 100 ng/ml or in a concentration of between about 4×10^{-6} and 4×10^{-3} nmol/ml.

Dinbergs *et al* teach a method for making a tissue engineering scaffold such as alginate/heparin-sepharose microsphere for inducing formation of extracellular matrix by cells such as endothelial cells and smooth muscle cells bound to said scaffold comprising coupling various matrix-enhancing molecule such as bFGF or TGFβ in a concentration 1-10 ng/ml (See Alginate/Heparin-Sepharose Microsphere Preparation and Growth Factor Incorporation, page 29823, column 2, bridging page 29824 column 1, in particular). The reference TGFβ is effective to elicit production of extracellular matrix (see page 29822, column 2, last paragraph, in particular) without increasing cellular proliferation (See Fig 2B, Fig 3B, Abstract, in particular). Dinbergs *et al* teach TGFβ has been incorporated into scaffold or various biodegradable polymer matrix such as collagen, hydrogel such as alginate, hydron (hyaluronic acid) and polyethylene glycol polymers (See page 29827, column 2, first full paragraph, in particular). Dinbergs *et al* teach TGFβ is useful for eliciting extracellular matrix formation without increasing cellular

proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute fibroblast as taught by the '849 patent for the smooth muscle cell or endothelial cells and matrix enhancing molecule TGFbeta at concentration 1-10 ng/ml as taught by Dinbergs *et al* for a method of for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells such as smooth muscle cell or endothelial cells where the TGF is covalently coupled to collagen or alginate via a polymer tethered as taught by the '430 patent, the '849 patent and Dinbergs *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Dinbergs *et al* teach TGFβ has been incorporated into scaffold or various biodegradable polymer matrix such as collagen, hydrogel such as alginate, hydron (hyaluronic acid) and polyethylene glycol polymers (See page 29827, column 2, first full paragraph, in particular) and that TGFβ is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular). The use of engineering scaffold is useful for controlling the cell number, the cell distribution and attachment in organ transplant as taught by the '849 patent. The method of tissue engineering is useful for tissue or organ implantation or tissue regeneration as taught by the '430 patent (see col. 4, line 28-40, in particular).

Applicants' arguments filed 1/30/06 have been fully considered but are not found persuasive.

Applicants' position is that the proposed combination of the '430 patent, the '849 patent and Dingers is improper because the examiner has not provided a sufficient teachings, suggestion, or motivation in the prior art to make such combination as discussed above.

In response, claim 24 does not recite the specific concentration such as ng/ml or nmol/ml of the specific matrix-enhancing molecule. Further, the specific type of cell attached to the engineering tissue scaffold that affected by the specific matrix enhancing molecule is not recited in claim 24.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that references cannot be arbitrarily combined and that there must be

some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In this case, the teachings of Dinbergs *et al* pertaining to TGFβ has been incorporated into scaffold or various biodegradable polymer matrix such as collagen, hydrogel such as alginate, hydron (hyaluronic acid) and polyethylene glycol polymers and is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days when coupling to various polymer such as alginate hydrogel for a sustained release (See page 29825, Fig 3A, in particular), the teachings of the '430 patent pertaining to a method of making a tissue engineering scaffold by providing a scaffold such as collagen (col. 4, lines 5-6, in particular) covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol (see PEG, col. 5, lines 32-55, in particular) covalently coupled to a matrix enhancing molecule such as TGFbeta (col. 6, line 58, see entire document, col. 8, General Method, Examples 1 and 6, col. 19, in particular) or insulin like growth factor or combination thereof (see col. 6, line 63, in particular) would have led one of ordinary skill in the art at the time the invention was made to make any tissue engineering scaffold with the expectation that at such concentration, it would elicit extracellular matrix formation without increasing cellular proliferation as taught by Dinbergs et al. One of ordinary skill in the art at the time the invention was made would expect that TGF beta is useful for inducing differentiation of fibroblast cells, a growth inhibitor of keratinocytes and endothelial cells, while ascorbic acid and TGFbeta1 increase collagen biosynthesis as taught by the '849 patent (see col. 12, lines 57-67, Table 1, in particular).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 170 USPQ 209 (CCPA 1971).

16. Claims 24 and 30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat 5,162,430 (Nov 10, 1992; PTO 892) in view of Scott-Burden et al (J Cardiovasc Pharmacol 16 Suppl 4: S36-41, 1990; PTO 892).

The teachings of the '430 patent have been discussed supra.

The claimed invention in claim 30 differs from the teachings of the reference only in that the method wherein the matrix-enhancing molecule is angiotensin II instead of TGF beta.

Scott-Burden et al teach angiotensin II activates the synthesis of extracellular matrix such as glycopeptides and proteoglycans by smooth muscle cells and growth of smooth muscle cell (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute TGFbeta as taught by the '430 patent for the angiotensin II as taught by Scott-Burden et al for a method of for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells such as smooth muscle cell where the angiotensin II is covalently coupled to collagen or alginate via a polymer tethered as taught by the '430 patent, the '849 patent and Scott-Burden et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because angiotensin II activates the synthesis of extracellular matrix such as glycopeptides and proteoglycans by smooth muscle cells and growth of smooth muscle cell as taught by Scott-Burden et al (see abstract, in particular). The method of tissue engineering is useful for tissue or organ implantation or tissue regeneration as taught by the '430 patent (see col. 4, line 28-40, in particular).

Applicants' arguments filed 1/30/06 have been fully considered but are not found persuasive.

Applicants' position is that the combination of the '430 Patent and Scottmurden has not been shown to teach or suggest the step of "covalently coupling the matrix-enhancing molecule to the scaffold, wherein the matrix-enhancing molecule is present at a concentration sufficient to elicit production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached ce1," as recited in Applicants' independent claim 24.

In response, instant claim 24 does not recite the specific concentration such as ng/ml or nmol/ml of the specific matrix-enhancing molecule. Further, the specific type of cell attached to the engineering tissue scaffold that affected by the specific matrix enhancing molecule is not recited in claim 24.

In contrast to applicants' assertion that the '403 does not teach the "step of covalently coupling of the matrix-enhancing molecule to the scaffold", the '430 patent teaches a method of making a tissue engineering scaffold by providing a scaffold such as collagen (col. 4, lines 5-6, in particular) covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol (see PEG, col. 5, lines 32-55, in particular) covalently coupled to a matrix enhancing molecule such as TGFbeta (col. 6, line 58, see entire document, col. 8, General Method, Examples 1 and 6, col. 19, in particular) or insulin like growth factor or combination thereof (see col. 6, line 63, in particular).

The claimed invention in claim 30 differs from the teachings of the reference only in that the method wherein the matrix-enhancing molecule is angiotensin II instead of TGF beta.

Scott-Burden et al teach angiotensin II activates the synthesis of extracellular matrix such as glycopeptides and proteoglycans by smooth muscle cells and growth of smooth muscle cell (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute TGFbeta as taught by the '430 patent for the angiotensin II as taught by Scott-Burden et al for a method of for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells such as smooth muscle cell where the angiotensin II is covalently coupled to collagen or alginate via a polymer tethered as taught by the '430 patent, the '849 patent and Scott-Burden et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because angiotensin II activates the synthesis of extracellular matrix such as glycopeptides and proteoglycans by smooth muscle cells and growth of smooth muscle cell as taught by Scott-Burden et al (see abstract, in particular). The method of tissue engineering is useful for tissue or organ implantation or tissue regeneration as taught by the '430 patent (see col. 4, line 28-40, in particular). Accordingly, the combined teachings of the '430 Patent and Scott-Burden et al teaches or suggests every limitation of Applicants' independent claim 24 and dependent claim 30.

17. Claims 24 and 34 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat 5,162,430 (Nov 10, 1992; PTO 892) in view of WO 94/23740 (of record, Oct 1994, PTO 1449) or WO 96/27657 (Sept 1996; PTO 1449).

The teachings of the '430 patent have been discussed supra.

The claimed invention in claim 34 differs from the teachings of the reference only in that the method wherein the scaffold is hyaluronic acid or polyethylene glycol polymers.

The WO 94/23740 publication teaches a method for making a tissue engineering scaffold comprising coupling various matrix-enhancing molecules such as TGFβ or TGFβ2 covalently coupling to polyethylene glycol (See page 12, line 11, PEG-TGF-β conjugates, rhTGF- TGF-β2 (PEG5000) bridging page 13, in particular). The WO 94/23740 publication teaches the method of making a tissue engineering scaffold comprising coupling TGFβ to a polymer is useful for stimulation of bone formation at a lower dose (See abstract, in particular).

The WO 96/27657 publication teaches a method for making a tissue engineering scaffold comprising coupling various matrix-enhancing molecules such as TGFβ (see page 10, claim 25 of WO 96/27657 publication, in particular) covalently coupled to a scaffold such as hyaluronic acid (see page 7, line 1, in particular) or collagen, or polyethylene oxide, or alginate, (See page 17, line 8, in particular). The WO 96/27657 publication teaches the growth factor is localized to desired target cell population and significantly less growth factor is needed to exert a biologic response (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the collagen and TGF beta in the tissue engineering scaffold comprising collagen covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol and matrix enhancing molecule such as TGFbeta as taught by the '430 patent for the polyethylene glycol as taught by the WO 94/23740 publication or the hyaluronic acid or polyethylene oxide, or alginate as taught by the WO 96/27657 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because polyethylene glycol covalently to TGFβ2 is useful for stimulation of bone formation at a lower dose as taught by the WO 94/23740 publication (See abstract, in particular). The WO 96/27657 publication teaches hyaluronic acid (see page 7, line 1, in particular) or polyethylene oxide, or

alginate coupled to TGFβ is useful for localized the desired target cell population and significantly less growth factor is needed to exert a biologic response (See abstract, in particular).

Applicants' arguments filed 1/30/06 have been fully considered but are not found persuasive.

Applicants' position is that the combination of the '430 Patent and WO 94/23740 or WO 96/27657 has not been shown to teach or suggest the step of "covalently coupling the matrix-enhancing molecule to the scaffold, wherein the matrix-enhancing molecule is present at a concentration sufficient to elicit production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cells" as recited in Applicants' independent claim 24. The '430 Patent has not been shown to disclose, teach, or suggest, either expressly or inherently, that "covalently coupling the matrix-enhancing molecule to the scaffold, wherein the matrix-enhancing molecule is present at a concentration sufficient to elicit production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cell," as recited in Applicants' independent claim 24. The Examiner relies on WO 94/23740 or W0 96/27657 for the teaching that "the scaffold is hyaluronic acid or polyethylene glycol polymers." (Office Action at 14.) Accordingly, the Examiner has not shown that the combination of the '430 Patent and WO 94/23740 or WO 96/27657 teaches or suggests every limitation of Applicants' independent claim 24 and dependent claim 34; and thus the '430 Patent and WO 94/23740 or WO 96/27657 combination cannot be used to obviate Applicants' claims 24 and 34.

In response, instant claim 24 does not recite the specific concentration such as ng/ml or nmol/ml of the specific matrix-enhancing molecule. Further, the specific type of cell attached to the engineering tissue scaffold that affected by the specific matrix enhancing molecule is not recited in claim 24.

In contrast to applicants' assertion that the '403 does not teach the "step of covalently coupling of the matrix-enhancing molecule to the scaffold", the '430 patent teaches a method of making a tissue engineering scaffold by providing a scaffold such as collagen (col. 4, lines 5-6, in particular) covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol (see PEG, col. 5, lines 32-55, in particular) covalently coupled to a matrix enhancing molecule such as TGFbeta (col. 6, line 58, see entire document, col. 8, General Method, Examples 1 and 6, col. 19, in particular) or insulin like growth factor or combination thereof (see col. 6, line 63, in particular).

The claimed invention in claim 34 differs from the teachings of the reference only in that the method wherein the scaffold is hyaluronic acid or polyethylene glycol polymers.

The WO 94/23740 publication teaches a method for making a tissue engineering scaffold comprising coupling various matrix-enhancing molecules such as TGFβ or TGFβ2 covalently coupling to polyethylene glycol (See page 12, line 11, PEG-TGF-β conjugates, rhTGF- TGF-β2 (PEG5000) bridging page 13, in particular). The WO 94/23740 publication teaches the method of making a tissue engineering scaffold comprising coupling TGFβ to a polymer is useful for stimulation of bone formation at a lower dose (See abstract, in particular).

The WO 96/27657 publication teaches a method for making a tissue engineering scaffold comprising coupling various matrix-enhancing molecules such as TGFβ (see page 10, claim 25 of WO 96/27657 publication, in particular) covalently coupled to a scaffold such as hyaluronic acid (see page 7, line 1, in particular) or collagen, or polyethylene oxide, or alginate, (See page 17, line 8, in particular). The WO 96/27657 publication teaches the growth factor is localized to desired target cell population and significantly less growth factor is needed to exert a biologic response (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the collagen and TGF beta in the tissue engineering scaffold comprising collagen covalently coupled to a polymer tether such as hydrophilic polymer polyethylene glycol and matrix enhancing molecule such as TGFbeta as taught by the '430 patent for the polyethylene glycol as taught by the WO 94/23740 publication or the hyaluronic acid or polyethylene oxide, or alginate as taught by the WO 96/27657 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because polyethylene glycol covalently to TGFβ2 is useful for stimulation of bone formation at a lower dose as taught by the WO 94/23740 publication (See abstract, in particular). The WO 96/27657 publication teaches hyaluronic acid (see page 7, line 1, in particular) or polyethylene oxide, or alginate coupled to TGFβ is useful for localized the desired target cell population and significantly less growth factor is needed to exert a biologic response (See abstract, in particular). Accordingly, the combined teachings of the '430 Patent and WO 94/23740 or WO 96/27657 teaches or suggests every limitation of Applicants' independent claim 24 and dependent claim 34.

18. No claim is allowed.

19. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

21. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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